REMARKS

In the Specification

The citation for Reference #68 has been amended to replace the hyperlink with the actual citation for the article. Support for the amendment is found in the copy of references provided with the Information Disclosure Statement. No new matter is presented.

Entry thereof is requested.

In the Claims

Applicant had elected claims 1-23 for examination in the response to the restriction requirement issued October 12, 2004. The Examiner also withdrew claims 14-17 and 20-23 from examination without stating the reasons for the withdrawal.

A review of claims 15-17 show that they are directed to an immunostimulatory complex wherein the peptide antigen is derived from HIV CD4 and claims 22 and 23 are directed to an immunostimulatory complex wherein the peptide antigen is derived from IgE. To simplify the examination, Applicant agrees to the withdrawal of claims 15-17 and 22-23 without prejudice to the filing of a divisional application thereof. However, claim 14 depends on claim 12 and claim 20 depend on claim 19 which are being examined and should be included in the group of claims being examined. These claims belong to this group and no additional search is required. Applicant requests the re-joining of claims 14 and 19 with the present group.

Claims 1, 4-10, 12-14 and claims 18 - 20 are amended to more clearly and particularly claim the invention. Claim 1 and the claims dependent thereon have been amended to particularly point out that the invention is for a stabilized immunostimulatory complex that is in microparticulate form. Support for the recital " immunostimulatory microparticulate complex" is found particularly in paragraphs [0134], [0173] of the specification. The microparticulate complex is made from a cationic immunogen complexed to CpG oligonucleotide and that the cationic immunogen is a peptide comprising a target B cell antigen or a CTL epitope and a T

helper cell epitope. This is supported by originally filed claim 3. Claim 18 is amended to more clearly define the cationic immunogen as a synthetic peptide wherein LHRH is conjugated to a T helper cell epitope. Claims 19 and 20 are amended to recite that the cationic immunogen is selected from the group consisting of SEQ ID NO: 7, 8, and 9 and a mixture thereof. Support is found in the originally filed claims 18, 19 and 20. More specifically, support for the amendment is found in the specification at page 44, [0132] and Table 1 describing three peptides wherein LHRH is conjugated to a T helper cell epitope. Entry of the amendment is requested.

The amendment of the claims is to more clearly define the invention. There is no intention of narrowing the scope of the invention claimed. To one of skill in the art of immunology, it is known that an immunogen comprises a B cell antigen or a CTL epitope and a T helper cell epitope. Applicant also wish to point out that the immunostimulatory complex is in microparticulate form as stated in the specification. Thus, claim 1 is not narrowed by the amendment.

RESPONSE

Objection to the specification and the Information Disclosure Statement

The Examiner objected to the specification and the Information Disclosure Statement for containing a hyperlink. This has been deleted and replaced with the citation for reference #68. A copy of the reference was provided to the Examiner in the binders containing the entire set of references cited in the specification. The objection is now moot.

Rejections

The claims have been rejected on four grounds, each of which is responded to in turn as follows.

Under 35 USC §112

Claim 18 is rejected as being indefinite for reciting 'the cationic peptide immunogen be derived from LHRH'. Claim 18 has been amended to define the cationic immunogen as a synthetic peptide wherein LHRH is conjugated to a T helper cell epitope.

Applicant wish to point out that the cationic peptide immunogen is defined in the specification and in claim 19 as being SEQ ID NO: 7, 8 or 9. Each of these peptides comprise LHRH conjugated to a T helper epitope. This definition is clear. Applicant believes that as amended the rejection of claim 18 on this ground is overcome.

Rejection Under 35 USC §102

Claims 1, 2, 7-13 and 18 are rejected as being anticipated by Krieg et al., WO 01/22972.

The Examiner contends that Krieg et al. teaches an anionic CpG oligonucleotide with is identical to SEQ ID NO:1, which has 32 nucleotides. The Examiner also contends that the mixture of anionic CpG oligonucleotide with Leuprolide acetate with a charge of +1 inherently form a complex. The Examiner concludes that for these reasons, Krieg et al anticipates claim 1, 2, 7-13 and 18.

Firstly, Krieg et al. describes pyrimidine rich (Py-rich) or TG nucleotides, and CpG oligonucleotides as being effective in activating an innate immune response by itself. Krieg et al. teaches that CpG oligonucleotide including SEQ ID NO:1 alone as being able to provoke an immune response. See Page 2, lines 17-32 and Page 16, lines 23-32 of Krieg et al.

Krieg et al does teach that the innate immune response generated is of assistance in the treatment of cancer, or for prevention of infection. In each case, the Py-rich, TG nucleotides, or CpG oligonucleotide is administered to stimulate the innate immune response and with an anti-cancer agent for the treatment of cancer. See page 14, line 31 to page 16, line 14. Krieg et al also teaches that the Py-rich or

TG nucleotide or CpG oligonucleotide can be administered with a cancer vaccine, such s EGF, Gp75 antigen, Ovarex, M-Vax, etc. See page 16, lines 15-20. Or with an antiviral agent. See, page 17, lines 1-11. Or with an anti-parasitic composition for treatment of parasitic infection. See, page 17, lines 12-17. Or with a composition for the treatment of allergies. There is nothing in Kreig et al to suggest that the Py-rich, TG nucleotides or CpG oligonucleotide form a complex with the anti-cancer therapeutic compositions, the cancer vaccines, the anti-viral agents, anti-parasitic agents or compositions for the treatment of allergies.

Applicant would like to point out that Krieg et al disclosed the administration of the Py-rich or TG nucleotides with the administration of leuprolide acetate identified as an anti-cancer agent. There is no teaching or suggestion that leuprolide acetate is an immunogenic peptide. In fact, it is known that leuprolide acetate is a LHRH agonist. It is a chemotherapeutic agent. It is not an immunogen. Leuprolide acetate itself is not immunogenic, just as LHRH itself is not immunogenic. See GP Talwar, Human Reproduction Update, 1997, 3:301-310 at 307, which states that LHRH

> **"Being a short peptide and also a 'self' hormone, it must be linked to a carrier in order to render it immunogenic."**

A copy of Talwar is enclosed.

It is clear that Krieg et al. does not describe, teach or suggest that leuprolide acetate is an immunogen. It describes leuprolide acetate as a LHRH agonist.

As amended claim 1 recites a stabilized immunostimulatory microparticulate **complex.** This complex is formed from a combination of a cationic peptide immunogen, comprising a target B-cell antigen or a CTL epitope and a T helper cell epitope, and an anionic CpG oligonucleotide. The claim is not directed at co-administration of CpG nucleotide with a peptide. Krieg et al. teaches co-administration. There is no teaching, description or suggestion of the formation of a complex, a chemical combination of CpG nucleotide with a peptide immunogen. The co-administration of leuprolide acetate with CpG oligonucleotide does not form a complex.

Whereas, claim 1 and the claims dependent thereon requires the formation of a microparticulate complex of the CpG oligonucleotide with an immunogenic peptide wherein LHRH is conjugated to a T helper cell epitope. Krieg et al. does not mention T helper cell epitopes anywhere in his specification or claims. Thus, it is clear that Krieg et al. does not teach or suggest the invention of claim 1 and cannot be regarded as anticipatory of the invention of claim 1 and the claims dependent thereon.

The Examiner suggest that Krieg et al. disclosed a mixture of leuprolide acetate with CpG oligonucleotide. However, Krieg et al. did not. Krieg et al taught co-administration. Therefore, Krieg et al does not and cannot be regarded to teach the formation of an immune stimulatory complex as suggested by the Examiner. Kreig et al. teaches clearly that the CpG oligonucleotide is co-administered with leuprolide acetate. There is nothing to indicate that a complex is formed. Moreover, since leuprolide acetate is not immunogenic and is not conjugated to a T helper cell epitope, it is not a cationic immunogen as defined by the claims.

Under the law, each and every element of a claimed invention must be found in one single reference before anticipation can be found. The rejection of claims 1, 2, 7-13 and 18 should be withdrawn in view of the amendment of claims 1, 7-13 and 18.

Rejection Under 35 USC §103

The Examiner rejected claim 3-6 and 19 as being obvious in view of a combination of Krieg et al and Ladd et al. US 5,759,551.

Claim 1 has been amended to include the limitation of claim 3 wherein the cationic immunogen is a synthetic peptide wherein a B cell antigen, a CTL epitope is conjugated to a T helper cell epitope. Claim 3 has been cancelled for being redundant. Therefore, the rejection is regarded as being directed to Claim 1 and the claims dependent thereon.

The Examiner states that claim 19 is directed to a peptide immunogen, SEQ ID NO:9 and a mixture of peptide immunogens. Applicant wishes to point out that

claim 19 is directed to an immunostimulatory complex of a peptide immunogen, SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID NO: 9 or a mixture thereof wherein the peptide immunogen is complexed with a CpG oligonucleotide.

The Examiner admits that Krieg et al. does not teach a peptide immunogen having the sequence of SEQ ID NO: 9. However, it is the Examiner's contention is that Krieg et al. which teaches the use of CpG oligonucleotides in conjunction with anti-cancer agents to increase the responsiveness of the anti-cancer therapy. And, that Ladd et al. disclosed a peptide immunogen comprising LHRH conjugated to a T-cell epitope and that one of those peptide immunogens is identical to SEQ ID NO:9. Because of this, one of ordinary skill in the art would be motivated to combine Krieg et al.'s teaching of CpG oligonucleotide with SEQ ID NO:9 in view of Ladd et al. to increase anti-cancer therapy.

A review of Krieg et al. shows that Krieg et al. taught that CpG nucleotide alone stimulates innate immune response and that it is advantageous to co-administer CpG oligonucleotides with anti-cancer therapeutic agents for the treatment of cancer. An anti-cancer agent is one that is used to treat a patient with cancer.

Ladd et al. disclosed LHRH-Th peptides as a vaccine. It is disclosed that the peptide vaccine is given to non-diseased animals or humans to produce antibodies to LHRH to prevent prostate cancer. It is important to recognize that a cancer prevention agent is used to prevent cancer. It is generally not regarded as an anti-cancer agent.

Moreover, as pointed out above, the claimed invention is directed at a complex, a chemical entity formed between the cationic immunogenic peptide and the anionic CpG oligonucleotide. Specific conditions are used to form the complex which is microparticulate. See page 43 [0128] to [0131], and page 45, Example 1 and Table 3 of the specification. Contrary to the Examiner's contention, there is no ergo formation of the complex merely with co-administration of a CpG oligonucleotide and leuprolide acetate. Neither Krieg et al. nor Ladd et al. disclosed, taught or suggest the formation of a complex. There is no motivation to form a

complex. There is no motivation to use the Ladd et al peptide immunogen to form a complex with the CpG oligonucleotide of Krieg et al when there is no teaching, no suggestion in Krieg et al. with respect to the formation of a complex.

The law is clear that a finding of obviousness cannot be based on a hindsight analysis of Applicant's disclosure and apply it to the prior art. Obviousness may only be found based on what is taught and suggested in the prior art itself. For this reason, claims 1, 4-6, and 19 as amended cannot be regarded as obvious in light of a combination of Krieg et al and Ladd et al and the rejection on this basis should be withdrawn.

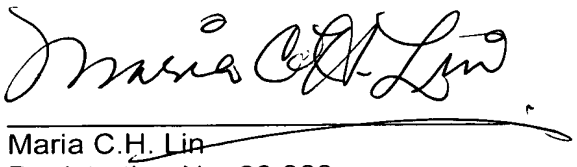
Double Patenting

The Examiner has also made a provisional rejection for double patenting in view of the continuation-in-part application filed subsequently. Applicant intends to delete the duplicative claims from the continuation-in-part application when such claims have been granted.

CONCLUSION

No other issues are presented. It is believed that the claims, 1, 4-10, 12-14 and 18-20 as amended are allowable. An early allowance is requested.

Respectfully submitted,



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